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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,500	02/01/2002	Avi J. Ashkenazi	P3130R1C7	5350

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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,500	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-47,50-52 and 56-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-47,50-52 and 56-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/5*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 20, 2005 has been entered.

Response to Amendment

2. Claims 40-47, 50-52 and 56-72 are under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on October 20, 2005 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

6. Claims 40-47, 50-52 and 56-72 stand rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility for those reasons of record in previous office actions of record.

At pages 3-4 of the Response, Applicant first reviews case law pertinent to the utility requirements and refers to the appropriate section of MPEP as well as to Utility Examination

Guidelines. Applicant further refers to case law to support the statement that in order to satisfy the utility requirement, "utility need not be proved to a statistical certainty" (pages 4-6, specifically at page 4). Applicant summarizes the evidence for the asserted utility of the claimed polypeptides as being "useful to treat tumors by affecting neovascularization and for the stimulation of angiogenesis" at page 6. Specifically, Applicant submits that "Applicants [...]provided reliable evidence that PRO444 stimulates *c-fos* in pericytes. [...] at the time the application was filed, in was well known that pericytes are involved in angiogenesis. Specifically, studies had shown that pericytes are present in newly formed capillary sprouts, and that pericytes are involved in later stages of angiogenesis, including survival of newly formed vasculature, for example by secretion of VEGF. [Also,] it was well known at the time the application was filed that VEGF is a potent angiogenic factor, and the VEGF expression is regulated by *c-fos*. [Accordingly,] the skilled artisan, like Applicants, would more likely than not believe that PRO444, as a stimulator of *c-fos* in pericytes, would be useful as a therapeutic target for pathological angiogenesis, as well as a tool for stimulating angiogenesis" (bottom at page 6). Applicant's arguments have been carefully considered but are not deemed to be persuasive for the following reasons.

The instant specification discloses structure of a novel polypeptide designated PRO444 of SEQ ID NO: 9 encoded by polynucleotide of SEQ ID NO: 8. The specification further discloses that polypeptide of SEQ ID NO: 9 "act[s] to induce the expression of c-fos in pericyte cells" (page 142, Example 60, assay 93). Based on this finding, the specification asserts that the instant polynucleotides encoding polypeptides of SEQ ID NO: 9 are "useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists

which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Induction of c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO[444] polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing the like".

As fully explained in the previous office actions of record, PRO444 polynucleotides cannot be used as markers for pericyte-associated tumors because there appears to be no disclosure that PRO444 is exclusively present/absent or expressed at the altered levels in pericyte-associated tumors. Further, the evidence presented in the instant specification as filed is inadequate to support a conclusion that PRO444-induced activation of expression of c-fos in pericytes is specifically related to angiogenesis. Therefore, the Examiner maintained that two of the Applicant's originally presented asserted utilities (as a marker for pericyte-associated tumors and for induction of angiogenesis in wound healing, for example) were not supported by the instant specification, as filed.

Beginning at page 7 of the Response, Applicant submits that at the time of the filing, the role of pericytes in angiogenesis was fully established and refers to articles by Nehls et al., Phodin et al. and Ozerdam et al (the last cited by the Examiner in the previous office action of record). First, it is important to clarify that the Examiner never disputed that pericytes have a role in angiogenesis. Anatomically, as a part of vasculature, pericytes are reasonably expected to play a significant role in formation of new blood vessels or angiogenesis. However, there appears to be no information available at the time of filing regarding their specific role in angiogenesis (see Applicant's cited art). Moreover, information presented in post-filing publication of Ozerdem et

al., 2003, clearly indicates that it is presently not fully understood if stimulation of pericytes results in up-regulation or down-regulation of vascularization (middle at page 8 of the Response). More importantly, the art at the time of invention does no substantiate the nexus between stimulation of c-fos in pericytes and their involvement, positive or negative, in angiogenesis (see specifically Applicant's reasoning on pages 10-11 of the Response).

At page 8 and page 11 of the Response, Applicant reviews articles, which disclose role of VEGF on promoting angiogenesis. The Examiner agrees that the role of angiogenic factor VEGF is well established. There is also no dispute that the art at the time of filing discloses that pericytes could secrete VEGF. However and contrary to Applicant's statement ("*c-fos* stimulates VEGF expression" at page 11 of the Response), there appears to be no evidence of record to show that induction of c-fos in pericytes is directly and specifically associated with expression of VEGF.

Applicant argues at pages 10-11 that because *c-fos* encodes a subunit of the nuclear transcription factor AP-1 and because AP-1 plays a role in the expression of VEGF, then *c-fos* stimulates VEGF expression. Applicant's arguments as well as presented articles by Tischer et al, Shima et al. and Kolch have been fully considered but are not persuasive because the relationship between *c-fos* , AP-1 and VEGF expression is not obvious. Applicant's reasoning lacks support in the specification as originally filed and also in the publications of record because there appears to be no indication that induction of expression of *c-fos* protooncogene that is known to be induced by many cellular stimuli, including growth factors, cytokines, T-cell activators, UV irradiation, hypoxia and PMA (see reasoning in the previous office actions of record and also Orlandi et al., 1996, Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 1675-11680) leads

to stimulation of VEGF expression by means of AP-1 transcription factor. On the contrary, Orlandi et al. publication discloses that, for example, in fibroblasts VEGF expression is unaffected by *c-fos*.

Applicant further refers to the Declaration of Dr. Gerritsen (The Gerritsen Declaration) under 37 CFR 1.132 filed January 31, 2005 and to publications by Ellis et al. , Kirkpatrick and Willett et al. (pages 11-12 of the Response) . The Gerritsen Declaration was considered and answered in full in the previous office action of record. Briefly, the Declaration is insufficient to overcome the instant rejection because it does not provide support for relationship between expression of *c-fos* in pericytes and angiogenesis. With respect to the publications used in discussion on pages 12-13, Applicant is advised that the asserted utility of the claimed invention cannot be relied upon disclosure available after the filing date of the instant specification. It is a matter of law that the specific and substantial credible utility of the claimed invention must be fully disclosed at the time of filing. As such, the instant specification discloses induction of expression of *c-fos* in pericytes treated with polypeptide of SEQ ID NO: 9 but discloses no evidence or sound scientific reasoning to support the asserted utility that polynucleotides encoding polypeptides of SEQ ID NO: 9 could be useful in stimulation of angiogenesis. There is no disclosure found in the instant specification or in the prior art of record that would specifically substantiate the nexus between *c-fos* activation and expression of VEGF in pericytes or between *c-fos* activation in pericytes and angiogenesis.

Applicant's analysis of articles by Sakurai et al. (2002) and Otani et al. (2000) on pages 14-15 of the Response has been fully considered but is not persuasive. Contrary to Applicant's statement that "Sakurai et al. demonstrates that factors that stimulate *c-fos* in pericytes lead to

stimulation of VEGF" (bottom at page 14), information presented in publication of Sakurai et al. fully supports the Examiner's point that activation of *c-fos* is a non-specific immediate cellular response to plurality of different factors. For example, Sakurai et al. describes that expression of *c-fos* mRNA was induced by FCS (fetal calf serum) and various prostaglandins (see Figure 5); however, only PGD_2 affected the expression levels of VEGF mRNA (page 2779). Further, Otani et al. demonstrated that angiotensin II stimulated VEGF expression on pericytes (page 1192), and angiotensin II stimulated *c-fos* expression in pericytes (page 1195). There appears to be no conclusions made in Otani et al. publication to support an assertion that any factor that stimulates *c-fos* expression in pericytes also stimulates expression of VEGF. The Examiner strongly disagrees with Applicant's statement that "those skilled in the art would more likely than not believe that PRO444, as an inducer of *c-fos* in pericytes, would promote angiogenesis" (middle at page 15 of the Response). On the contrary, a skilled artisan, knowing that addition of fetal calf serum causes induction of *c-fos* (see Sakurai et al. above, for example), would readily appreciate that disclosure that PRO444 polypeptides are capable of stimulation of *c-fos* does not provide any meaningful or definitive evidence that PRO444 molecules could be used as therapeutics in treatment of pathological angiogenesis or any other clinical conditions.

The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA. *See In re Fisher,* 2005 WL 2139421 (Sept. 7, 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility" 2005 WL 2139421, at *4. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* At *5. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as

disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Id.*

Just as in *Fisher* case where the Board reasoned that use of the claimed ESTs for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," (*Id.*, slip op. at 15), in the instant case, in view of the absence of clear understanding of the relationship between polypeptide of SEQ ID NO: 9 and activation of *c-fos* and also what effect this might have on angiogenesis, the instant claimed polypeptide PRO444 is suitable only for additional research to identify or reasonably confirm a "real world" context of use.

Therefore, for reasons of record presented in the previous office actions and reasons fully explained above, the instant rejection of claims 40-47, 50-52 and 56-72 is maintained.

Claim Rejections - 35 USC § 112

7. Claims 40-47, 50-52 and 56-72 stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Claims 40-44 and 56-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention for those reasons of record as explained in the previous office actions of record.

To traverse the instant rejection, Applicant presents essentially the same arguments (pages 16-19 of the Response) that were fully considered and answered earlier in appropriate sections of the previous office actions of record.

At pages 19-20, Applicant refers to *In re Wallach* and argues that since the instant specification "disclosed SEQ ID NOs: 8 and 9, and claims nucleic acids which are at least 80% identical to them or nucleic acids which encode them, and which meet the functional limitation of encoding a polypeptide that stimulates *c-fos* in pericytes" (bottom at page 19), then the requirements of 112, first paragraph, written description are met. Applicant's arguments have been fully considered but are not persuasive for the following reasons.

With respect to *In re Wallach* decision, the Examiner fully agrees that listing of every polynucleotide that meets the limitations presented in the claims 40-44 is not required to satisfy written description requirement. However, as fully explained in the previous communications of record, the only two molecular embodiments that are disclosed in the instant specification as originally filed are limited to polynucleotide of SEQ ID NO: 8 and polypeptide of SEQ ID NO: 9. Knowing that stimulation of *c-fos* expression represents a non-specific cellular response (see reasons of record in appropriate sections related to lack of utility of the instant invention), one skilled in the art clearly cannot rely on the assay disclosed in Example 60 of the instant specification (top at page 20 of the Response) to distinguish which molecular embodiments that demonstrate at least 80% structural similarity to the polynucleotide encoding polypeptide of SEQ ID NO: 9 are encompassed by the instant claims. Thus, the instant specification fails to provide

written description of the claimed polynucleotides so that a skilled artisan can envision the detailed chemical structure of what is claimed.

Conclusion

9. No claim is allowed.

10. This is a continuation of applicant's earlier Application No. 10/066,500. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

November 16, 2005